REMARKS

Claims 15-17, 25, and 29-34 are pending. The claims have been amended to place them in condition for allowance.

Restriction Requirement

Applicants reiterate their belief that the restriction requirement is not proper. It is well established that the Office may not restrict a single claim into multiple inventions, as the Office has done here. See *In re Weber*, 580 F.2d 455, 458-59 (CCPA 1978) ("If . . . a single claim is required to be divided up and presented in several applications, that claim would never be considered on its merits. The totality of the resulting fragmentary claims would not necessarily be the equivalent of the original claim. Further, since the subgenera would be defined by the examiner rather than by the applicant, it is not inconceivable that a number of the fragments would not be described in the specification ... [A] rejection under § 121 [restriction practice] violates the basic right of the applicant to claim his invention as he chooses.")

Drawings

Replacement drawings will be submitted in a Supplemental Amendment.

Objection to Claim 30

Claim 30 was objected to as not further limiting claim 29, from which it depends. Applicants respectfully traverse. The Office states "neither the prior art or the specification teach AT domains which are specific to malonyl, ethylmalonyl, or 2-hydroxymalonyl." Applicants disagree. "Methylmalonyl specific" AT domain encoding nucleic acids are described in the specification at page 29, lines 5-10. Applicants respectfully submit that AT domains with substrate specificity are well known in the art. A copy of an article discussing substrate specificity (Hadock et al. 1995, "Divergent sequence motifs correlated with the substrate specificity of (methyl)malonyl-CoA:acyl carrier protein transacylase domains in modular polyketide synthases" *FEBS Lett.* 374:246-8) is attached for the Examiner's convenience. If the Examiner believes a

telephone discussion concerning this objection (or any other matter) would advance the prosecution he is invited to contact the undersigned.

Rejections Under Section 112, Second Paragraph

The rejections under 35 USC 112, paragraph 2 are obviated by the amendments of claims 15, 25, 30, 31 and 34. These amendments are made to solely for clarity and not to change the scope of the claims.

Rejections Under Section 103

Claims 15-17, 25 and 29-34 were rejected as allegedly obvious in view of U.S. Pat. No. 6,355,459 ("Schupp"), U.S. Pat. No. 6,391,594 ("Khosla A") and WO 97/02358 ("Khosla B"). Applicants respectfully traverse.

The Schupp reference provides nucleotide sequence of the *Sorangium cellulosum* epothilone synthase gene cluster and proposes functions for the encoded proteins, but does not describe the compounds epothilone C and D and, moreover, erroneously teaches that an exogenous (non-cluster) gene product (a methyltransferase) is required to form epothilone B. The pioneering Khosla A reference provides guidance for manipulation, modification, and expression of polyketide synthases generally, but does not describe the epothilone PKS gene cluster, modified epothilone synthases, or epothilone biosynthesis. The Khosla B reference describes synthesis of modified polyketide synthases using cell-expression systems, but does not describe the epothilone PKS gene cluster, modified epothilone synthases, or epothilone biosynthesis.

The claims are to a PKS comprising a modified EpoE. The claimed modified synthase produces results and compounds that would not have been expected from the Schupp reference combined with the teachings of the KhoslaA or Khosla B references. The claims now recite that the modified PKS produces an epothilone D derivative in a non-*Sorangium* host cell. Because the Schupp reference teaches that a non-epothilone gene cluster methyltransferase gene is required to place the C-12 methyl in epothilone B and does not even mention epothilone D (which Applicants teach is a precursor of epothilone B), the combination of references cited by the Examiner would not have led the ordinarily skilled artisan to believe that epothilone D derivatives could be produced in

non-*Sorangium* heterologous host cells using an epothilone PKS with a modified *epoE* gene. Instead, such artisans would have believed that it was impossible to make epothilone B (much less epothilone D) in a heterologous host using the PKS genes described by the Schupp reference.

The present specification provides guidance for making modified epothilone synthases and teaches that such synthases are useful for production of epothilone D derivatives. In contrast, the Schupp reference, while providing sequences corresponding to the epothilone synthase, did not teach what products would be produced by the epothilone PKS in the absence of post-synthesis modification by polyketide modifying enzymes. For example, with regard to epothilone A, the Schupp specification contains disclosure relating to formation of an epothilone in which the "redox state" of the C-3 (column 34, lines 3-28), C-5 (see column 33, line 22-52), and C-12 (see column 32, lines 48-64) carbons of the epothilone macrolactone ring might require "adjustment" by the EPO F gene product (which generally corresponds to the *epoK* gene product in the instant specification) to be identical to epothilone A. While the Schupp reference states that "the nascent polyketide chain of epothilone corresponds to epothilone A" (see column 32, lines 58-59), the specification of the Schupp reference creates considerable uncertainty as to what is meant by "corresponds" in this context due to the uncertainty regarding the "redox state" at C-3, C-5, and C-12, and the role of the "EPO F" gene in the "adjustment of the redox state" at one or more of those positions (see column 34, lines 43-48). Similarly, the Schupp patent attributes the origin of the C-12 methyl group that characterizes epothilone B (and therefore, as the instant specification but not the Schupp reference taught, epothilone D) as "requiring a post-PKS C-methyltransferase activity." See column 32, lines 59 through 61, of the Schupp reference. The Schupp reference did not disclose the production of epothilone B and epothilone D by the epothilone synthase (teaching instead that a hypothetical post-PKS C-methyltransferase is required) and did not disclose or suggest that epothilone D derivatives would be produced by a modified epothilone synthase. In contrast, the present inventors disclosed that a product of the epothilone synthase was epothilone D, and that useful derivatives of epothilone D could be made using a synthase comprising a modified EpoE protein that lacks certain β-carbonyl modifying activities of the native protein.

The present inventors provide specific guidance about the results of particular modifications of the *epoE* gene (see, e.g., pages 41-55 of the specification) and thus provide motivation *not found* in the cited references to make such modifications and, further, an expectation of success *not found* in the cited references that such a modification will produce a PKS encoding epothilone derivatives. In addition to not providing motivation to make a PKS comprising a modified EpoE protein that lacks certain β-carbonyl modifying activities, the references relied on by the Office provide no expectation of success. Both the motivation to modify and any expectation that such modification will be successful require an understanding of the properties of the epothilone synthase. As discussed above, the Schupp reference does not provide an expectation of success because (1) there is no teaching as to what epothilone would be produced by the unmodified PKS, and (2) there is teaching away from the expectation that derivatives of epothilone D (taught by the present specification) would be produced by a PKS comprising a modified EpoE protein. Applicants respectfully submit that a combination of references, which the Examiner asserts (but the Applicants do not concede) together merely suggest that modifications in the epothilone synthase *can* be made, does not render obvious the specific modified PKSs taught by the present inventors to produce derivatives of epothilone D.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

Applicants have, by way of the amendments and remarks presented herein addressed all issues that were raised in the outstanding Office Action. Applicants respectfully submit that this Amendment has demonstrated there is no legal basis for the rejections and so that the pending claims are in condition for allowance. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 300622003111. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: October 22, 2003

Respectfully submitted,

By _____

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Encls. (Hadock et al. 1995, *FEBS Lett.* 374:246-8)